REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-21 are pending. Applicants elect with traverse Group I (claims 1-19) for examination on the merits. Applicants reserve the right to prosecute nonelected subject matter in a further patent application. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry.

Notwithstanding the above election, reconsideration of the restriction requirement is requested because examination of all pending claims would not constitute a serious burden. Although the inventions identified by the Examiner are separately patentable, both the need for compact prosecution and the public interest would be served by examination of all claims in a single application. Thus, claims 19-21 should not be withdrawn from consideration.

In the alternative, Applicants disagree with the allegation in the Action that the pending claims lack unity of invention, and therefore belong to different groups of inventions. Although they agree with the Examiner's conclusion that the inventions are separately patentable, Applicants' traversal is based on the pending claims being so linked as to form a single general inventive concept under PCT Rule 13.1. Therefore, the pending claims should be examined together in this application.

Applicants submit that, pursuant to the *Manual of Patent Examining Procedure* (M.P.E.P.), the claims identified by the Examiner as Groups I to III are linked to form a single general inventive concept. In particular, the Examiner's attention is directed to M.P.E.P. § 1850 III A Combinations of Different Categories of Claims (8th Ed., Rev. 5, August 2006), which states at 1800-96 to 1800-97:

> The method for determining unity of invention under Rule 13 PCT shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:
>
> (A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product . . .
>
> [A] process shall be considered to be specially adapted for the manufacture of a product if the claimed process inherently results in the claimed product with the technical relationship being present between the claimed product and claimed process. The words "specially adapted" are

not intended to imply that the product could not also be manufactured by a different process.

It was alleged in the Action that the inventions listed by the Examiner as Groups I to III do not relate to a single general inventive concept because they lack the same or corresponding special technical features over Garcia et al. (Biotecnologia Aplicada 12: 152-155, 1995). In accordance with the section of the M.P.E.P. quoted above, Group I (claims 1-18) is directed to a process "specially adapted" for a product's manufacture, Group II (claims 19-20) is directed to the product, and Group III (claim 21) is directed to a method of using the product. The Examiner alleged in the Office Action that Garcia et al. disclose a process in which human IFN alpha 2b was produced by cultivating the recombinant protein in *Pichia pastoris* yeast. But the special technical feature linking the pending claims in this application is the selection of specific media alone or in combination with other strategies like the use of particular feeding strategy during growth and production phase, as has been employed in the present invention, which has important effect over the final yield of protein as well as the ease of the process etc.

The special technical features of the present invention lie in the optimization of various parameters, conditions etc., like the media to be used, the pH, the fermentation process, etc. Here, Applicants found that using complex media, defined salt media, or a combination of complex and defined media; supplementing the media with glycerol feed; starving the cells prior to separation; etc. provides a process for high expression of IFN-alfa-2b. These special technical features are neither taught nor suggested in the cited document. In particular, Applicants' invention differs from what was disclosed in the cited document as follows:

1. Applicants may employ BGY or a defined medium during growth phase and BMY during production phase, while Garcia et al. use G0 medium.

2. Garcia et al. describe the separation and purification step after the production phase, which is well known in art and is commonly used to obtain the desired product. But Applicants may perform the separation step between the growth phase and production phase, which is not described in the cited document.

3. During the sterile cell separation, Applicants do not require washing of the cells after centrifugation. Washing at larger scale will take more time as one step is added in

the process. Moreover, like sterile cell separation, it is also not risk free in terms of risk of contamination.

4. Applicants may continuously supplement with glycerol during the growth phase while Garcia et al. only supplement once during the growth phase.

5. Applicants may keep the methanol concentration between 0.5 to 3.0% (v/v) by stopping the methanol feed when 3% concentration was achieved and subsequent addition of methanol was started only when methanol concentration dropped to about 0.5 to 0.8 % (i.e., discontinuous feed). Garcia et al. only maintain methanol concentration at 0.4% to obtain maximal expression of recombinant protein. But such a concentration level would be useful only for a narrow range of cell mass culture. In the event of the cell mass in the fermentor increasing beyond this range, the prior art concentration would yield sub-optimal expression.

6. The unique induction strategy that may be used with Applicants' invention is different from that reported in Garcia et al. and is one of the reasons for high expression of protein. Development of a discontinuous methanol supply which provides induction such that it will give the maximum expression at a higher biomass level is novel and not suggested in the cited document.

7. Applicants' invention may be practiced by increasing the starvation period by 0.5 to 1 hour before the production phase to increase the yield of protein whereas the cited document does not mention using a starvation period.

Applicants earnestly solicit an early and favorable examination on the merits. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100